

## **REMARKS**

### **Priority**

Priority for the claimed invention is found throughout provisional patent application 60/080,321. At for example, paragraph 4, line 1 through line 13; paragraph 5, line 1 through line 6; paragraph 6, line 1 through line 3; paragraph 7, line 1 through line 5; paragraph 8, line 1 through line 4; paragraph 9, line 1 through line 16; paragraph 10, line 6 through line 11; Table 1; Figure 2; Figure 3; Figure 4; and Figure 5.

### **Anticipation of claims 4-14**

Claims 4-14 are novel over Manoharan. Claim 4 is directed to oligonucleotides having one or more POPS blocks flanked by regions of at least two contiguous 2'-O-substituted ribonucleosides. Manoharan does not teach this feature. As described in the DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS, Manoharan teaches that "The present invention provides oligonucleotides that contain at least one region of 2'-modified nucleosides connected by alternating phosphodiester and phosphorothioate linkages." Thus, Manoharan teaches oligonucleotides in which the regions of 2'-modified nucleosides are connected by alternating phosphodiester and phosphorothioate linkages, not in which the intervening deoxynucleotides are connected by alternating phosphodiester and phosphorothioate linkages, as in claim 4 and its dependent claims 5-14. The oligonucleotide pointed out by the Examiner (SEQ ID NO. 2) more particularly points out this difference. That oligonucleotide has a region of phosphorothioate linked deoxynucleotides flanked by oligonucleotide regions having 2'-modified nucleosides linked by alternating phosphodiester and phosphorothioate linkages.

Accordingly, claims 4-14 are novel over Manoharan. Applicants therefore respectfully request that this rejection be withdrawn.

### **Obviousness of claims 15-25**

As noted by the Examiner, claims 15-25 are directed to inverted hybrid oligonucleotides comprising a region of 2'-O-substituted ribonucleosides flanked by regions of deoxynucleosides

linked by alternating phosphorothioate and phosphodiester linkages. While acknowledging that this particular arrangement is not specifically disclosed by Manoharan, the rejection describes the claimed invention as a “mere design choice based on Manoharan’s teaching”. However, as described above, the primary teaching relied upon from Manoharan is incorrect. Whether in the hybrid or inverted hybrid configuration, Manoharan teaches only oligonucleotides in which the 2’-modified regions are linked by alternating phosphorothioate and phosphodiester linkages, not in which the deoxynucleotides are linked by alternating phosphorothioate and phosphodiester linkages. Accordingly, Manoharan cannot suggest the invention of claims 15-25.

As further evidence of this, the Examiner’s attention is directed to Column 10 of Manoharan, which states that “oligonucleotides of the present invention which have a uniform alternating phosphodiester/phosphorothioate backbone ... do not function by a RNase H dependent mechanism, but rather primarily ... by a translation arrest mechanism.” This is because such oligonucleotides have 2’-modifications, which are known to not serve as a substrate for RNaseH. Clearly, in the oligonucleotides of claims 15-25, the region containing alternating phosphodiester/phosphorothioate linkages does act through an RNase H mechanism. This is not contemplated by Manoharan because Manoharan deals exclusively with alternating phosphodiester/phosphorothioate linkages exclusively in the context of non-RNase H-activating 2’-modified nucleotides.

For these reasons, claims 15-25 are nonobvious and patentable over Manoharan. Accordingly, Applicants respectfully request that this rejection be withdrawn.

**Provisional obviousness-type double patenting**

As noted above, Applicants believe that this reply overcomes the rejection of claims 4-14 for anticipation as well as the rejection of claims 5-25 for obviousness. Thus, this remains the only rejection of claims 4-11. Accordingly, Applicants respectfully request that this rejection be withdrawn.

**Conclusion**

For the reasons set forth above, claims 4-25 are patentable and ready for allowance. Applicants respectfully request that notice of such allowance be provided. If the Examiner believes that any discussion of this communication would be useful, the Examiner is invited to contact the undersigned attorney by telephone at 781-933-6630.

Respectfully submitted,

Date: May 30, 2006

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